

Depression and Diastolic Hypertension: A Female-specific role of thyroid dysfunction in NHANES and LEMON Studies

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Title: Depression and Diastolic Hypertension: A Female-specific role of thyroid dysfunction in NHANES and LEMON Studies

Abstract

The role of stress-induced thyroid dysfunction in the development of hypertension remains unclear. We tested whether thyroid status modifies or mediates the relationship between psychological distress and blood pressure in sex-stratified two independent cohorts. The NHANES thyroid module (N = 8,310; 4,177 men, 4,133 women; United States, 2007-2012) provided depression (PHQ-9), T3, T4, and blood pressure. The LEMON study (N = 227; 145 men, 82 women; Germany) provided trait anxiety, perceived stress, Hamilton depression, TICS chronic-stress subscales, TSH, and blood pressure. We tested sex-stratified moderation and mediation hypotheses for the effect of thyroid variables on the association between psychological distress and blood pressure, followed by the subgroup analysis. The odds of diastolic hypertension comorbid with hypothyroidism in NHANES women with depression was OR=2.22 (95% CI: 1.46-3.36, p=0.0002). Depression was inversely associated with free T4 ($\beta = -0.027$, $p = 0.017$) and total T4 ($\beta = -0.028$, $p = 0.029$), each predicted diastolic BP ($\beta = -0.081$ and -0.062 , both $p < 0.001$), with a significant mediation effect (ACME = 0.00215 & 0.00174 respectively, $p < 0.05$). In LEMON women, TSH positively moderated the effect of Hamilton depression and chronic worrying on diastolic BP (β interaction = 0.213 and 0.207, $p < 0.05$); within the high-TSH subgroup, both independently predicted diastolic BP ($\beta = 0.307$ and 0.248, $p < 0.05$). However, there were neither moderated nor mediated effects of thyroid variables in men. Analysis reveals a potential Female-specific role of thyroid function in linking depression to elevated diastolic blood pressure, indicating a thyroid-vascular axis in women.

Keywords: chronic stress; depression; hypothalamic-pituitary-thyroid (HPT) axis; moderation; causal mediation; hypothyroidism; hypertension

Highlights:

- Thyroid hormones correlated with blood pressure in both sexes; however, the thyroid-mediated effect on blood pressure was significant only in women.
- In men, no thyroid moderation or mediation of the depression-to-blood pressure relationship reached significance, despite robust thyroid-to-blood pressure correlations and regressions.

- In NHANES women, depression suppressed free T4 and total T4; depressed women had higher diastolic BP; and reduced T4 with a statistically significant ($p < 0.05$) mediated effect of depression on diastolic blood pressure.
- In LEMON women, TSH moderated the effect of depression and chronic worrying on diastolic blood pressure (β interaction = 0.213 and 0.207; $p < 0.05$), with both stressors predicting higher diastolic BP in the high-TSH subgroup ($\beta = 0.307$ and 0.248; $p < 0.05$).

Introduction

Cardiovascular disease remains the leading cause of global mortality, with ischemic heart disease and stroke among the top causes of death worldwide (GBD 2019) (Vos et al., 2020). Hypertension, the largest single contributor to this burden, is a well-established risk factor for ischemic heart disease, stroke, chronic kidney disease, and dementia (Beaney et al., 2020; Vos et al., 2020; Zhou et al., 2021). Psychological stress has emerged as a key driver of hypertension, disrupting cardiovascular regulatory pathways (Fontes et al., 2023; Sara et al., 2022; Vaccarino & Bremner, 2024). While acute stress responses are physiologically adaptive, repeated or unresolved psychosocial stressors can transition into chronic states that compound cardiovascular risk over time (Kumar et al., 2022; Rohleder, 2019). Identifying exactly how this transition occurs remains one of the clinical gaps in psychiatry research (Rohleder, 2019). Among the psychological factors shaping this trajectory, anxiety disorders stand out as a particularly significant yet underexplored contributor, with wide-ranging interactions across metabolic and endocrine systems. Anxiety disorders affect approximately 301 million individuals globally, with a lifetime prevalence of 30.5% in women versus 19.2% in men (ratio 1:1.7), a disparity that persists across most anxiety subtypes (Javaid et al., 2023; McLean et al., 2011). Unlike acute stress, anxiety disorder persists as an anticipatory state independent of identifiable threats, producing sustained cardiovascular consequences that accumulate over time (Daviu et al., 2019).

Depression independently raises hypertension risk. A meta-analysis of prospective cohort studies (22,367 participants, mean follow-up 9.6 years) found that depression increased the risk of incident hypertension by 42% (adjusted RR = 1.42, 95% CI 1.09-1.86) (Meng et al., 2012), and a recent 36-study meta-analysis confirmed the association (pooled OR = 1.20, 95% CI 1.09-1.32; longitudinal HR = 1.28, 95% CI 1.16-1.41) (Satapathy et al., 2025). In NHANES specifically, depressive symptoms have been linked to higher hypertension prevalence and poorer blood pressure control in US adults (Fang et al., 2022), with diastolic blood pressure showing a non-linear association with depression severity (Zhang et al., 2024).

Psychological stress is also associated with thyroid dysfunction. Prospective data show that anxiety significantly raises the risk of both hypothyroidism and hyperthyroidism, with anxiety severity positively correlated with thyroid disease risk (Fan et al., 2024). Among hypothyroid patients, 63% exhibit anxiety symptoms, with higher rates in females (65.72%) than males (56.66%) (Bathla et al., 2016). Chronic stress-induced cortisol elevation suppresses TSH secretion and impairs T4 to T3 conversion via the hypothalamic-pituitary-thyroid (HPT) axis (Helmreich et al., 2005). Thyroid hormones, in turn, modulate key neurotransmitters, including serotonin and GABA, and their dysregulation creates reciprocal pathways between anxiety and thyroid pathology that further compromise autonomic and cardiovascular regulation (Wu et al., 2021).

Psychosocial stress is associated with TSH elevation (H. Hong & Lee, 2022; Kyriacou et al., 2023), and individuals reporting stress symptoms face higher odds of thyroid disease (adjusted OR = 2.38, $p = 0.002$) (Voulgari et al., 2022). Perceived stress correlates directly with TSH (Chaudhuri & Koner, 2020; Kautzky et al., 2022), PTSD predicts hypothyroidism in a dose-dependent manner in women (Jung et al., 2019), and night shift work raises TSH (Leso et al., 2020). In a psychiatric cohort, women with suppressed TSH had 3.53 times the odds of depression (95% CI 1.37-9.10), and those with elevated TSH nearly twice the odds (OR 1.95, 95% CI 1.02-3.73), with no such associations in men (Baweja et al., 2026).

Thyroid dysfunction adds another layer to CVD risk, with over 200 million people diagnosed with thyroid disorders worldwide (Koutsouleris et al., 2022), with women and vulnerable groups bearing a disproportionate share of this burden. The cardiovascular system is targeted by thyroid hormone action, partly owing to the presence of thyroid hormone receptors in myocardial and vascular tissue, which renders cardiac function highly sensitive even to subtle hormonal shifts and related cardiovascular risk (Kuś et al., 2021; Razvi et al., 2018). Hypothyroidism independently predicts elevated blood pressure (Piantanida et al., 2016), and impaired thyroid hormone sensitivity, reflected by a higher Thyroid Feedback Quantile-Based Index (TFQI), was significantly associated with elevated systolic ($\beta = 3.22$), diastolic ($\beta = 2.32$), and mean arterial pressure ($\beta = 2.62$) and increased arterial stiffness and hypertension risk (OR 1.27, $p = 0.006$) among 6,272 participants (Yang et al., 2022).

Taken together, psychological stress and anxiety are established risk factors for hypertension and are also associated with alterations in thyroid hormone levels and TSH. However, whether HPT-axis dysregulation links the effects of stress and anxiety on blood pressure, whether by moderating or mediating them, remains unknown. Women carry a disproportionate burden of both stress-related disorders and thyroid disease, yet

cardiovascular risk in this group is rarely examined through an endocrine lens. If disrupted thyroid function connects psychological stress to blood pressure dysregulation, serum TSH and thyroid hormones in anxious or depressed women may signal cardiovascular risk well before hypertension develops. Testing this hypothesis requires both moderation and causal mediation approaches and validation across independent populations, neither of which prior studies have attempted. We assessed depression (PHQ-9), thyroid hormones (TSH, free T4, total T4, free T3, total T3), and BP in NHANES, and Hamilton depression, trait anxiety, perceived stress, chronic-stress subscales, TSH, and BP in LEMON, applying sex-stratified moderation and mediation analyses to determine whether a hypothyroid state marks the condition under which psychological stress raises BP in both men and women.

1. Materials and Methods

1.1. Study Design and Populations

This study employed a cross-cohort comparative design that integrated data from two independent population cohorts: the National Health and Nutrition Examination Survey (NHANES) thyroid module in the United States (Refer to **Table 1** for the detailed population characteristics) and the Leipzig Study for Mind-Body-Emotion Interactions (LEMON) in Germany. All statistical analyses were conducted using R version 4.2.2 .

1.2. NHANES Cohort: Sample Selection and Data Integration

The NHANES thyroid dataset encompassed 8,310 adults (4,177 men, 4,133 women) from three survey cycles (2007-2012) with population-representative sampling (CDC(US) & NCHS, n.d.). Depression was assessed using the Patient Health Questionnaire-9 (PHQ-9) (Kroenke et al., 2001). The PHQ-9 generates scores ranging from 0 to 27, with higher scores indicating greater symptom severity. Thyroid function was measured by immunoassay (TSH, total T3, total T4, free T3, free T4). Blood pressure was recorded as three consecutive seated measurements; mean systolic and diastolic BP were used in all analyses to reduce measurement variability.

1.3. LEMON Cohort: Characteristics

The LEMON study provided data from 227 healthy adults (145 men, 82 women) in Leipzig, Germany, in two age strata (20-40 years, n=153; 55-80 years, n=74), excluding ages 40-55 (Babayan et al., 2019). Psychological stress was measured using the Perceived Stress Questionnaire (PSQ) and the Trier Inventory for Chronic Stress (TICS), which yielded subscale scores for Work Overload, Pressure to Perform, Work Discontent, Work

Demands, Social Overload, Social Tension, Social Isolation, Lack of Social Recognition, Chronic Worrying, and a screening scale as well as TICS-OVERALL score (average of all ten subscales). The anxiety score was reported using the State-Trait Anxiety Inventory. Blood pressure was recorded before (BP1) and after (BP2) the MRI session at the left arm, with an additional right-arm reading at BP1 to rule out pathological inter-arm differences. Readings were retained separately rather than averaged, as BP1 and BP2 reflect physiologically distinct pre- and post-MRI states.

1.4. Data Preprocessing

Redundant columns and variables exceeding 10% missingness were removed. The remaining missing values were imputed using k-nearest-neighbour imputation ($k = 5$). Outliers in thyroid and BP variables were removed using the Median Absolute Deviation criterion ($k = 4.5$) (Leys et al., 2013). All numeric variables were rescaled by robust-Z transformation $((x - \text{median})/\text{IQR})$. For NHANES, residual variation across the three survey cycles was removed using the ‘ComBat’ empirical Bayes method with survey year as the batch factor (Johnson et al., 2007), with key analytic variables protected. All analyses were conducted separately in men and women. Since thyroid hormone levels were not reported in LEMON data, only TSH was used for the mediation and moderation analysis.

1.5. Statistical Analysis

1.5.1. Group comparisons

The NHANES dataset were stratified by sex and the depressions status defined by PHQ scores as (non-depressed, PHQ-9 = 0; depressed, PHQ-9 = 10-27). The thyroid hormone status and blood pressure measures were compared between the depressed and non depressed groups using Wilcoxon test in R.

1.5.2. Spearman correlation and Multivariate regression analysis

Spearman's rank correlation coefficients were computed for pairwise combinations of thyroid, stress and BP variables within each cohort. Linear regression models assessed stress-thyroid-BP relationships, adjusted for age and BMI (LEMON) or age, BMI, and survey year (NHANES), stratified by sex. Predictors and outcomes were robust-Z scaled; β coefficients reflect change per IQR-equivalent shift.

1.5.3. Moderation analysis

To test whether thyroid status modifies the stress-to-BP relationship in the sex-stratified data, the multivariable linear models with a stress x thyroid variable interaction term were fitted: $BP = \beta_0 + \beta_1 \text{ Stress} + \beta_2 \text{ thyroid}$

variable + β_3 (Stress x thyroid variable) + covariates + error, with age and BMI as covariates and model-specific handling of missing data for each stress by BP pair. The interaction coefficient β_3 quantifies the moderation (Aiken, 1991; Hayes, 2017). A significant positive β_3 indicates that the slope of stress on BP becomes steeper as TSH rises or T3/T4 reduces, to identify whether high TSH or low T3/T4 levels relay the effect of stress on BP. To corroborate the moderation results, the data were partitioned into low, normal, and high thyroid groups using mean and standard deviation cut-offs (low: $< \mu - 1SD$, normal: $\mu \pm 1SD$, high: $\mu + 1SD$), and the regression of diastolic BP on each stress measure, adjusted for age and BMI, was estimated within each subgroup.

1.5.4. Causal mediation analysis

To test whether thyroid hormones mediate the effect of stress on blood pressure in the sex-stratified data, a causal mediation analysis was performed within the counterfactual framework using the R mediation package (Tingley et al., 2014), with stress or depression as the exposure, thyroid variables as the mediator, mean systolic or diastolic BP as the outcome, and adjustments for age, BMI, survey year, race/ethnicity, education level, family poverty-income ratio, pesticide use, and smoking status as covariates, using 1000 quasi-Bayesian simulations. The average causal mediation effect (ACME), average direct effect (ADE), and proportion mediated were estimated. Sensitivity to unmeasured confounding was assessed by the critical error correlation (ρ) at which the ACME equals zero (Carnegie et al., 2018). Group comparisons of thyroid hormones and blood pressure between non-depressed (PHQ-9 = 0) and depressed (PHQ-9 = 10 to 27) women, with 3 SD per-group outlier removal, used the Wilcoxon rank-sum test.

2. Results

2.1. Prevalence of diastolic hypertension and hypothyroidism in NHANES cohort

Among NHANES women (N = 4,133), N=1045 were stratified as non-depressed (PHQ-9 score=0) and N=551 as depressed (PHQ-9 score =10-27). Both free T4 and total T4 were significantly different between the groups (**Fig 1a**) with lower values in depressed group. Diastolic blood pressure was significantly higher in the depressed group. Hypertension and hypothyroidism prevalence, defined respectively as diastolic blood pressure exceeding 80 mmHg and free T4 below 0.8 ng/dL, both differed by depression status (**Fig 1a**). In Hypertension was present in 18.3% of depressed women (N = 99) compared with 11.1% of non-depressed women (N = 118) with an OR =1.72 (95% CI=1.29-2.3, p=0.0002), and hypothyroidism was present in 48.9% of depressed women (N = 264) compared with 40.7% of non-depressed women (N = 431) with an OR=1.31 (95% CI=1.06-1.61, p=0.01). The co-occurrence of both conditions was more than twice as common among depressed women

(9.3%, N = 50) as among non-depressed women (4.2%, N = 45) with an OR=2.22 (95% CI=1.46 - 3.36, p=0.0002) (**Fig 1b**).

2.2. Associations of Depression and thyroid hormone in the NHANES Dataset

In NHANES women (N = 4,133), depression was inversely associated with free T4 ($\beta = -0.027$, $p = 0.017$) and total T4 ($\beta = -0.028$, $p = 0.029$) and positively correlated with free T3 ($\rho = 0.038$, $p = 0.018$), while in men (N = 4,177) depression correlated inversely with systolic pressure ($\rho = -0.060$, $p < 0.001$) and positively with free T3 ($\rho = 0.035$, $p = 0.027$) (**Fig 2**). Group comparison in women confirmed the hypothyroid profile: depressed women (PHQ-9 = 10 to 27) had significantly lower free T4 ($p < 0.001$) and lower total T4 ($p = 0.015$) than non-depressed women (PHQ-9 = 0) (**Fig 1a**).

2.3. Associations of Thyroid Hormone with BP in the NHANES Cohort

Free T4 inversely predicted diastolic BP in women ($\beta = -0.081$, $p < 0.001$) and men ($\beta = -0.107$, $p < 0.001$), and TSH correlated positively with systolic and diastolic BP in both sexes (**Table 2, Fig 2**). Depressed women had higher mean diastolic BP than non-depressed women ($p = 0.048$) (**Fig 1a**). Among women with moderate-to-severe depression (PHQ-9 = 10-27), the depressed subgroup regression showed a consistent trend ($\beta = 0.206$, $p = 0.098$, N = 523). In the total NHANES cohort, depression showed a trend-level positive association with mean DBP ($\beta = 0.014$, $p = 0.156$). Free T3 positively predicted BP in both sexes, and total T4 inversely predicted diastolic BP in women ($\beta = -0.062$, $p < 0.001$).

2.4. T4 mediates the effect of depression on diastolic BP in women (NHANES)

In women, causal mediation analysis confirmed that thyroid hormone suppression mediated the effect of depression on elevation of diastolic BP. The analysis revealed only the mediated effect by free/total T4 was statistically significant (ACME = 0.00215 & 0.00174 respectively, $p < 0.05$, $\rho = -0.1$), whereas the direct and total effects were not statistically significant indicating a prominent mediation by thyroid function. As the proportion of total effect, Free and total T4 mediated 10-12% of the depression-to-diastolic BP effect (**Table 2**), however, the evaluation of the proportion of mediated effect remains unstable as the direct and total effects were not statistically significant. No systolic mediation or thyroid moderation was significant in NHANES; no mediation was significant in men.

2.5. Correlations of stress scales, TSH, and BP in LEMON Cohort

In LEMON men (N = 145), work-stress measures correlated positively with TSH ($\rho = 0.176$ - 0.266 , $p < 0.05$), while TSH correlated inversely with BP ($\rho = -0.328$ to -0.278 , $p < 0.001$). In women (N = 82), pressure to perform correlated with TSH ($\rho = 0.251$, $p = 0.024$) and lack of social recognition with diastolic BP ($\rho = 0.254$, $p = 0.023$) (Fig 3).

2.6. Multivariate regression analysis of BP on stress scales in LEMON data

In age and BMI adjusted regression, men showed two significant positive associations with diastolic BP, trait anxiety (BP2 left diastole $\beta = 0.148$, $p = 0.035$) and chronic worrying (BP2 left diastole $\beta = 0.129$, $p = 0.038$), and several trend-level positive associations at diastolic sites, including trait anxiety, TICS Screening Scale, Work Demands, and chronic worrying on right diastolic pressure ($\beta = 0.117$ to 0.143 , $0.072 \leq p \leq 0.088$). In women, lack of social recognition independently predicted higher diastolic BP (BP2 left diastole $\beta = 0.119$, $p = 0.043$), with trend-level positive associations for social isolation, work overload, social tension, and pressure to perform on left diastolic pressure and for PSQ overall and work discontent on right diastolic pressure ($\beta = 0.116$ to 0.189 , $0.050 \leq p \leq 0.095$). Across both sexes, all significant and trend-level associations were directed at diastolic BP; no stress measure predicted TSH after adjustment (Table 3, Fig 3).

2.7. TSH moderates the effect of stress on diastolic BP in women (LEMON)

In women (N = 82), moderation analysis identified TSH as a significant effect modifier of diastolic BP (Table 3). Hamilton depression interacted positively with TSH on diastolic BP (BP2 left diastole; β interaction = 0.213 , $p = 0.037$, 95% CI: 0.014 to 0.412), and TICS chronic worrying showed the same synergistic pattern (β interaction = 0.207 , $p = 0.043$, 95% CI: 0.006 to 0.407). In each model, the main effects of stress and TSH were non-significant, indicating that diastolic BP rose specifically when elevated stress interacted with elevated TSH. No thyroid moderation of the stress-to-BP relationship was significant in men. Subgroup regression reinforced this pattern. Partitioning women by TSH into low, normal, and high groups, both chronic worrying and depression independently predicted higher right diastolic BP within the high-TSH subgroup (chronic worrying: $\beta = 0.307$, $p = 0.010$, N = 13; Hamilton depression: $\beta = 0.248$, $p = 0.018$, N = 13), whereas neither association was significant in the normal-TSH (N = 52) or low-TSH (N = 15) subgroups. Diastolic BP was higher in the high-TSH than the normal-TSH subgroup (BP1 left diastole $p = 0.032$; BP2 left diastole $p = 0.017$; BP1 right diastole $p = 0.098$) (Fig 1c, Table 3). Mediation models in LEMON were not significant in either sex.

3. Discussion and Conclusions

Two independent cohorts converge on the finding that a hypothyroid state links psychological stress to diastolic hypertension, specifically in women. In NHANES, depression suppressed T4, and reduced T4 mediated the depression effect on diastolic BP. In LEMON, elevated TSH amplified the stress-diastolic BP relationship. The convergence of two thyroid markers and two analytic frameworks on the same female-specific diastolic signal identifies women in a hypothyroid state as the cardiovascularly vulnerable subgroup (**Fig 4**). Beyond demonstrating independent associations of depression with hypothyroidism and diastolic hypertension, we observed the strongest association for their coexistence. Together with our mediation and moderation analyses, these findings support the hypothesis that thyroid dysfunction represents a biological link between psychological distress and elevated diastolic blood pressure in women, rather than merely a coexisting co-morbidity.

3.1. Thyroid hormones mediate depression-induced diastolic hypertension

The depression-T4 suppression observed in NHANES women is consistent with central hypothyroidism, in which hypercortisolaemia suppresses TRH and impairs deiodinase activity (Barden, 2004; Mason & Pariente, 2006), or non-thyroidal illness syndrome driven by pro-inflammatory cytokines (Beurel et al., 2020; DeGroot, 2015; Sciacchitano et al., 2022). In men, depression related positively to free T3 but did not produce a hypothyroid T4 profile, and no mediation followed, consistent with functional hypothyroidism in women perpetuating depression (Wu et al., 2021) and elevating cardiovascular risk (Moon et al., 2018; Razvi et al., 2018). The predominance of the mediation effect on diastolic BP is consistent with reduced T4 impairing endothelial nitric oxide production and increasing vascular smooth-muscle contractility, mechanisms governing peripheral resistance and diastolic pressure (Cai et al., 2015; Dernellis & Panaretou, 2002; Razvi et al., 2018). The stronger mediation by free T4 reflects the biological importance of the unbound fraction (Mendel, 1989).

3.2. TSH as an effect modifier of psychological stress-related hypertension in LEMON women

In LEMON women, the stress-diastolic BP signal was conditional on TSH, with significant positive interactions and high-TSH subgroup effects. TSH carries dual information in a stressed woman: as a thyroid health indicator and as a cardiovascular risk modifier. Longitudinal evidence supports the plausibility of this view, since higher-normal TSH predicts incident hypertension over 5-year and 11-year follow-up with stronger associations in women (Asvold et al., 2013; Jiang et al., 2017; Liu et al., 2010). Whether interventions that lower cortisol (Rogerson et al., 2024) or normalise upper-range TSH (Bekkering et al., 2019) attenuate this stress-amplified diastolic risk is a directly testable hypothesis. TSH receptors in vascular tissue exert cardiovascular effects independent of circulating thyroid hormone (Alomair et al., 2024; Razvi et al., 2018), and elevated TSH

promotes endothelial dysfunction even within the euthyroid range (Neves et al., 2021; Yang et al., 2022), with stronger TSH-BP associations in women (Asvold et al., 2013; Liu et al., 2010). Sustained stress alters TRH-TSH dynamics and impairs T4-to-T3 conversion (Fischer et al., 2019; Helmreich et al., 2005), generating the high-TSH state in which stress raises diastolic BP. In men, work stress correlated positively with TSH, yet TSH correlated inversely with BP, highlighting the female specificity.

3.3. A convergent female-specific phenotype and sex differences

Although the two cohorts used different thyroid markers and psychological instruments, they converge on how thyroid status regulates the psychological stress-induced rise in diastolic BP in women, linking HPT-axis dysfunction with stress and diastolic hypertension. Suppressed T4 in NHANES and elevated TSH in LEMON are complementary biochemical signatures of a hypothyroid hormonal milieu, and in both, the moderation and mediation signals reached significance only with diastolic BP in women. However, in men, free T4 inversely predicted diastolic BP, and free T3 positively predicted BP in both sexes, suggesting that this effect is female-specific. Oestrogen amplifies HPA reactivity and cortisol-thyroid interactions, while testosterone dampens them (Bangasser & Valentino, 2014; Tahboub & Arafah, 2009), and X-linked immune regulation further heightens female susceptibility (Klein & Flanagan, 2016), providing a biological rationale for why the thyroid-conditioned stress-to-BP link emerges in women.

3.4. Strengths and Limitations

This study examined two independent cohorts with different designs and demographics, and cross-validated the findings. Full NHANES adjustment for socioeconomic and environmental confounders confirmed that the T4-mediated pathway persists independently of these factors. Sex-stratified analyses were essential, as pooling would have concealed the female-specific effects. Evidence of thyroid dysfunction following psychosocial stress (Chaudhuri & Koner, 2020; Fischer et al., 2019; Jung et al., 2019; Puttaswamy et al., 2024; Walter et al., 2012) and the independent association between thyroid dysfunction and hypertension in prospective studies (Asvold et al., 2013; Beaney et al., 2020; Jiang et al., 2017; Liu et al., 2010) support the biological coherence. Prospective confirmation is needed. However, there are contradictory reports in the literature, where the HUNT study found overt hypothyroidism associated with a lower likelihood of depression (Engum et al., 2002), Korean data linked subclinical hyperthyroidism rather than hypothyroidism to depression (J. W. Hong et al., 2018), and in young adults, the pattern differed by sex (Forman-Hoffman & Philibert, 2006). These inconsistencies likely reflect

differences in thyroid markers, depression definitions, age ranges, and sex stratification. NHANES used the PHQ-9 self-report, and neither cohort measured cortisol or CRH directly. Genetic background, early-life adversity, and chronic-versus-acute stress distinctions were not captured. The LEMON female sample was small (N = 82), and the 40-55 age gap spans perimenopause, a critical hormonal window. Healthy volunteer recruitment likely attenuated effect sizes.

3.5. Clinical Implications and Future Directions

These findings have direct clinical relevance. TSH in stressed or depressed women warrants attention as a cardiovascular vulnerability marker, particularly in the upper-normal range (Garber et al., 2012; H. Hong & Lee, 2022; Kyriacou et al., 2023), and free T4 should be assessed since suppression may go undetected with TSH alone (Garber et al., 2012). Whether thyroid supplementation reduces both BP and psychological symptoms is testable in randomized trials (Bekkering et al., 2019; Fan et al., 2024; Wu et al., 2021). Cardiovascular risk assessment in women should integrate psychological screening with thyroid function testing. Future prospective studies should test whether stress reduction and thyroid supplementation attenuate cardiovascular risk and identify genetically vulnerable subgroups.

Figure Legends

Fig 1. Group comparisons of diastolic BP, thyroid hormones, and BP by thyroid and depression status. (a)

In NHANES women (N = 4,133), depressed women (PHQ-9 = 10-27) had significantly lower free T4 ($p < 0.001$) and total T4 ($p = 0.015$) than non-depressed women (PHQ-9 = 0). Depressed women had significantly higher mean diastolic BP ($p = 0.048$); mean systolic BP did not differ significantly ($p = 0.093$). Blue, non-depressed or normal-TSH; red, depressed or high-TSH. Boxes show median and IQR; whiskers extend to 1.5 times the IQR. **(b)** Prevalence of hypertension and hypothyroidism by depression status: Grouped bar chart showing the percentage of participants meeting criteria for hypertension (diastolic blood pressure greater than 80 mmHg; red), hypothyroidism (free T4 less than 0.8 ng/dL; blue), and both conditions concurrently (purple), stratified by depression status. Bars show the percentage of each depression group meeting the stated criterion, with the number of affected participants (N) labeled above each bar. **(c)** In LEMON women (N = 65), the high-TSH subgroup had significantly higher diastolic BP than the normal-TSH subgroup at two readings (BP1 left diastole $p = 0.032$; BP2 left diastole $p = 0.017$).

Fig 2. Associations among depression, thyroid function, and BP in NHANES (N = 8,310; men = 4,177, women = 4,133). Forest plot of Spearman correlations (blocks 1 and 2) and age-, BMI-, and survey-year-adjusted regression coefficients (block 3) with 95% CIs. Only statistically significant associations are shown. Women in red, men in blue. The dashed line marks the null. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

Fig 3. Associations among psychological stress, TSH, and BP in LEMON (N = 227; men = 145, women = 82). Forest plot of stress-TSH Spearman correlations (block 1) and age and BMI-adjusted stress-to-blood-pressure regression coefficients (block 2) with 95% CIs. Women in red, men in blue. The dashed line marks the null. * $p < 0.05$; † trend (0.05 to 0.10). BP2 LD, second left diastolic; BP1 RD/LS, first right diastolic/left systolic.

Fig 4. Proposed model of HPT-axis dysregulation linking psychological stress to hypertension. Stress activates the hypothalamus, stimulating TRH and pituitary TSH secretion. Elevated TSH promotes thyroid hormone output; T4 exerts negative feedback on the hypothalamus and pituitary. Dysregulation of this axis, indexed by elevated TSH or suppressed T4, converges on hypertension. A direct stress-to-hypertension pathway (blue arrow) operates in parallel. (Created with BioRender.com.)

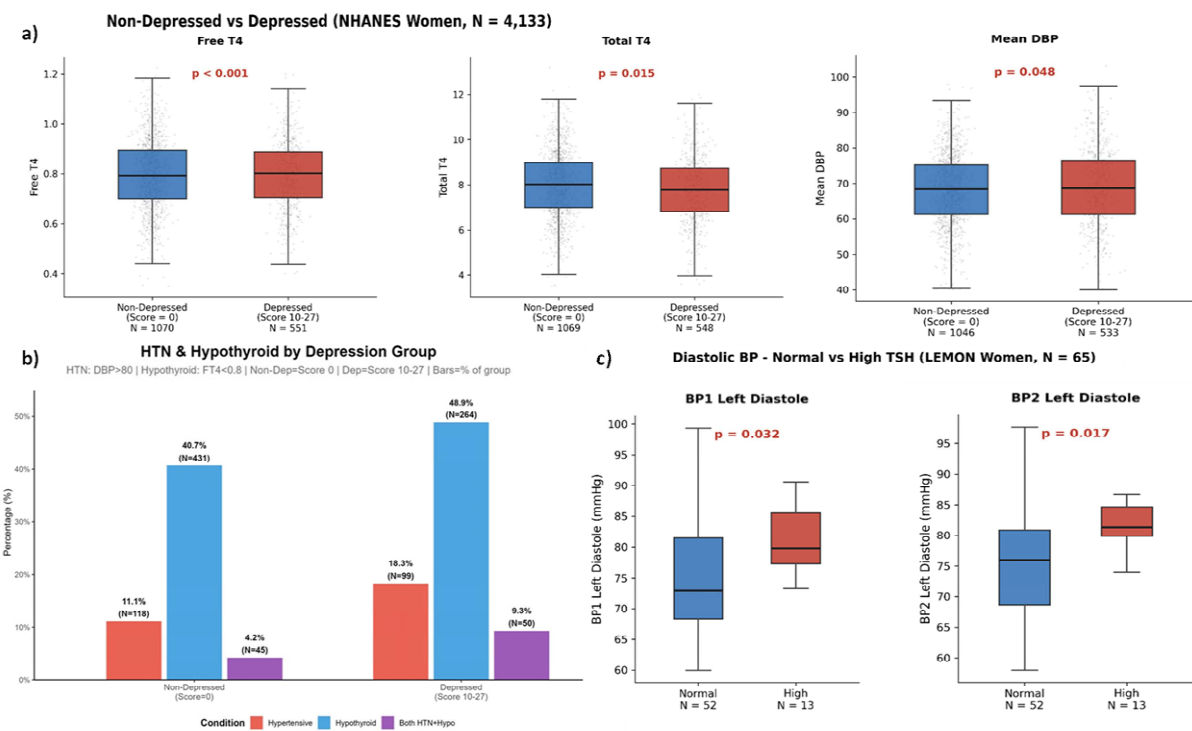


Fig 1. Group comparisons of diastolic BP, thyroid hormones, and BP by thyroid and depression status. (a) In NHANES women (N = 4,133), depressed women (PHQ-9 = 10-27) had significantly lower free T4 ($p < 0.001$) and total T4 ($p = 0.015$) than non-depressed women (PHQ-9 = 0). Depressed women had significantly higher mean diastolic BP ($p = 0.048$); mean systolic BP did not differ significantly ($p = 0.093$). Blue: non-depressed normal-TSH; red: depressed or high-TSH. Boxes show median and IQR; whiskers extend to 1.5 times the IQR. **(b)** Prevalence of hypertension and hypothyroidism by depression status: Grouped bar chart showing the percentage of participants meeting criteria for hypertension (diastolic blood pressure greater than 80 mmHg; red), hypothyroidism (free T4 less than 0.8 ng/dL; blue), and both conditions concurrently (purple), stratified by depression status. Bars show the percentage of each depression group meeting the stated criterion, with the number of affected participants (N) labelled above each bar. **(c)** In LEMON women (N = 65), the high-TSH subgroup had significantly higher diastolic BP than the normal-TSH subgroup at two readings (BP1 left diastole $p = 0.032$; BP2 left diastole $p = 0.017$).

Depression, Thyroid Function, and Blood Pressure in NHANES (N = 8,310; men = 4,177, women = 4,133)

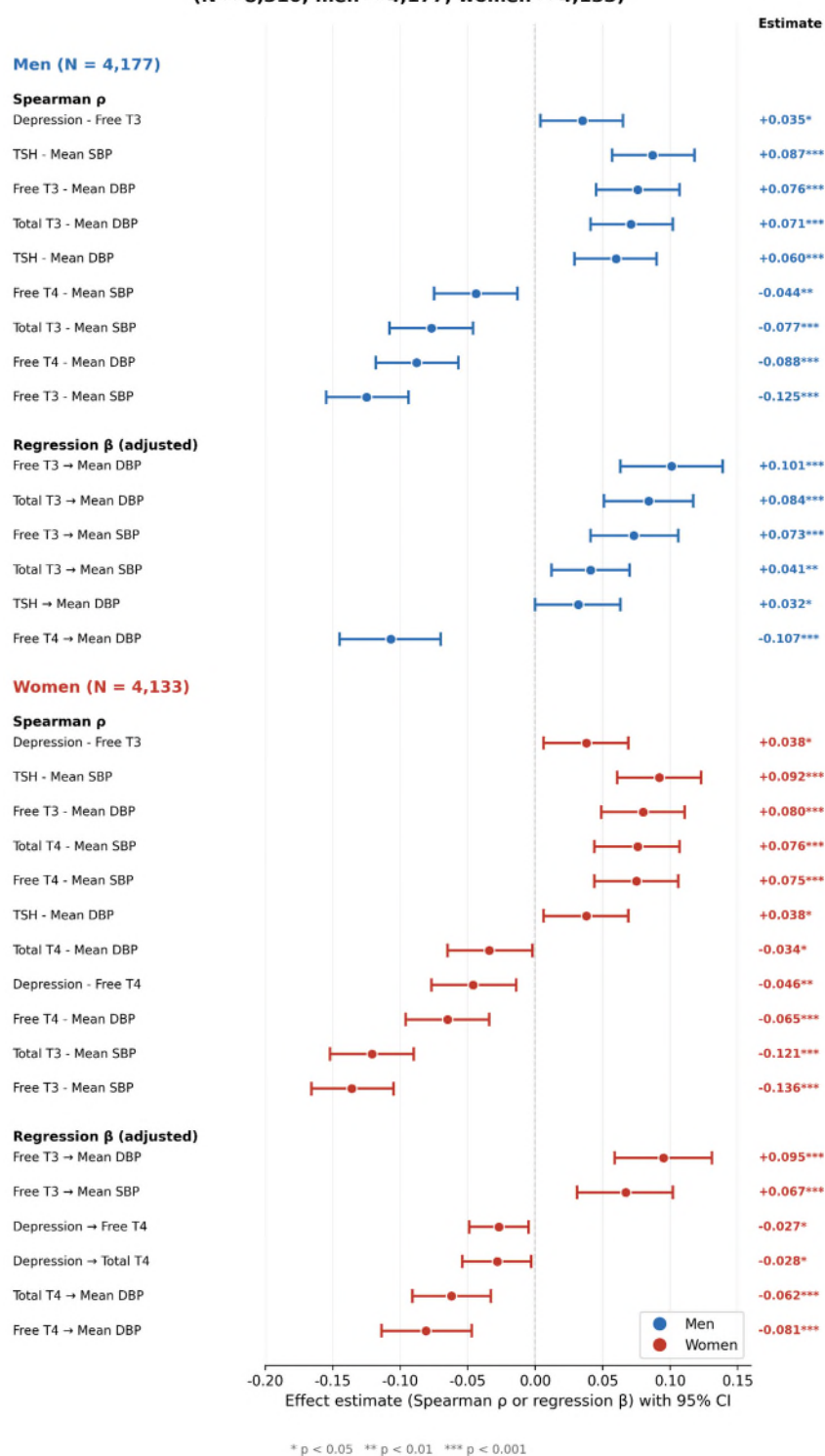


Fig 2. Associations among depression, thyroid function, and BP in NHANES (N = 8,310; men = 4,177, women = 4,133). Forest plot of Spearman correlations (blocks 1 and 2) and age-, BMI-, and survey-year-adjusted regression coefficients (block 3) with 95% CIs. Only statistically significant associations are shown. Women in red, men in blue. The dashed line marks the null. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

Stress, TSH, and Blood Pressure in LEMON (N = 227; men = 145, women = 82)

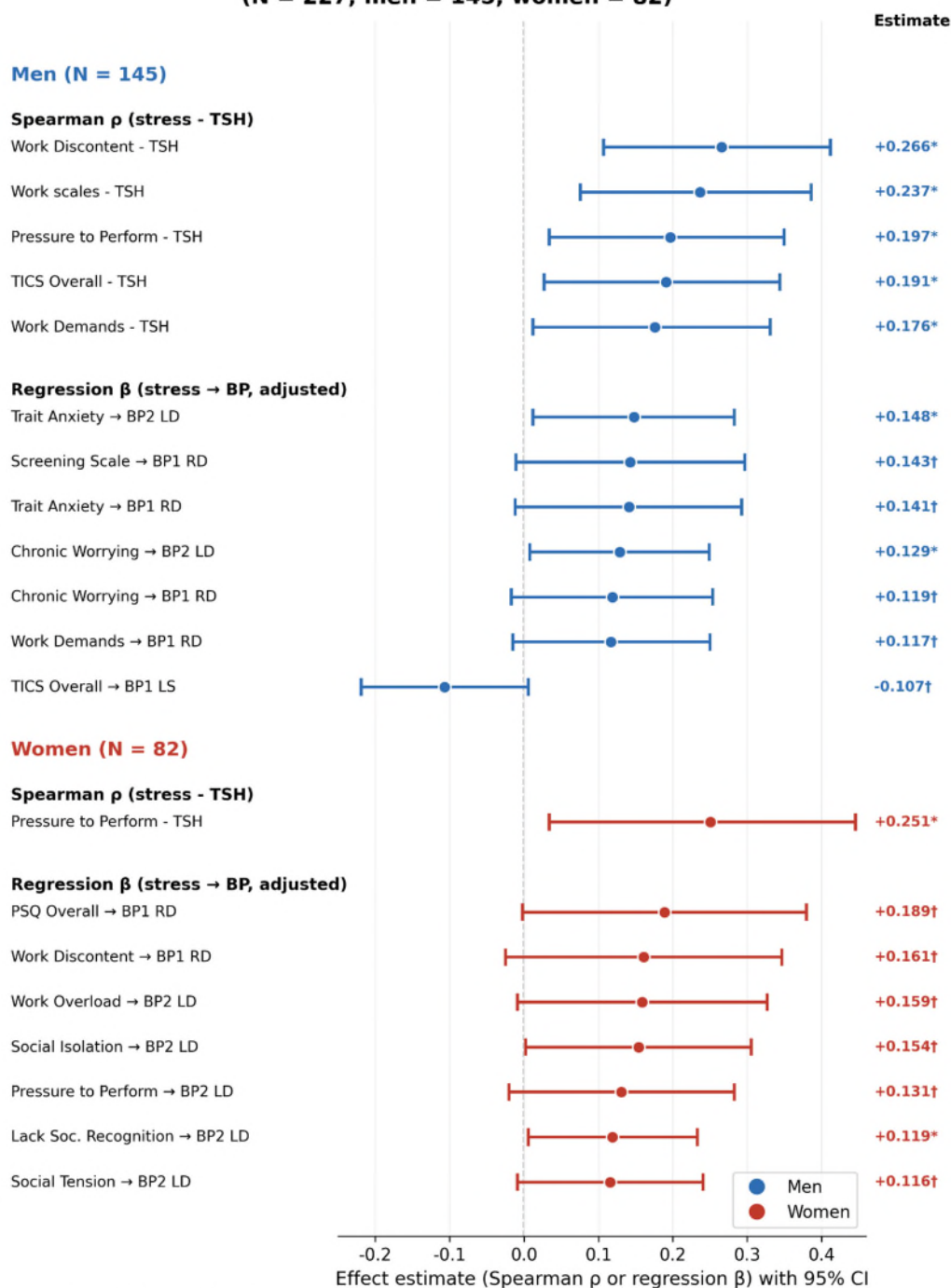
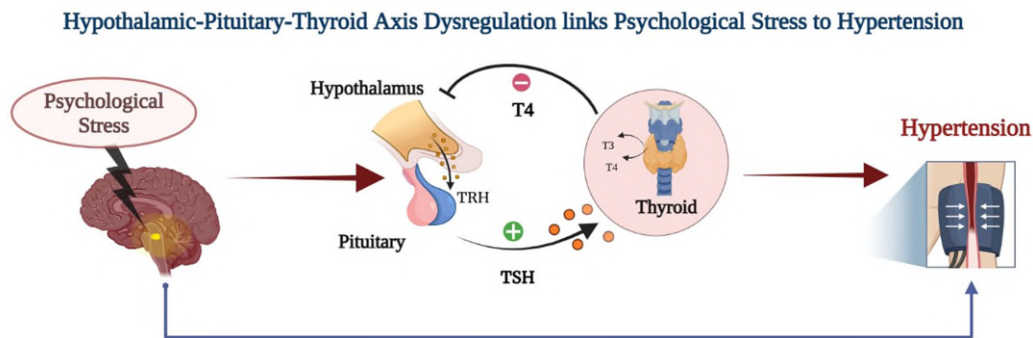


Fig 3. Associations among psychological stress, TSH, and BP in LEMON (N = 227; men = 145, women = 82). Forest plot of stress-TSH Spearman correlations (block 1) and age and BMI-adjusted stress-to-blood-pressure regression coefficients (block 2) with 95% CIs. Women in red, men in blue. The dashed line marks the null. * $p < 0.05$; † trend ($0.05 \leq p < 0.10$). BP2 LD, second left diastolic; BP1 RD/LS, first right diastolic / left systolic.

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394

395 **Fig 4. Proposed model of HPT-axis dysregulation linking psychological stress to hypertension.** Stress
396 activates the hypothalamus, stimulating TRH and pituitary TSH secretion. Elevated TSH promotes thyroid
397 hormone output; T4 exerts negative feedback on the hypothalamus and pituitary. Dysregulation of this axis,
398 indexed by elevated TSH or suppressed T4, converges on hypertension. A direct stress-to-hypertension pathway
399 (blue arrow) operates in parallel. (Created with BioRender.com.)

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402 **Table 1. Population Characteristics of the LEMON and NHANES Cohorts**

403 **A: NHANES Thyroid Module (United States, 2007-2012; N = 8,310)**

	Men (n = 4,177)	Women (n = 4,133)
<i>Demographics</i>		
Age (years)	48.34 ± 18.70	48.72 ± 18.41
BMI (kg/m ²)	28.57 ± 6.11	29.12 ± 7.36
<i>Race/Ethnicity</i>		
Mexican American	672 (16.1%)	708 (17.1%)
Other Hispanic	427 (10.2%)	502 (12.1%)
Non-Hispanic White	1957 (46.9%)	1876 (45.4%)
Non-Hispanic Black	838 (20.1%)	807 (19.5%)
Other/multi-racial	283 (6.8%)	240 (5.8%)
<i>Education Level, n (%)</i>		
< 9th grade	482 (11.5%)	438 (10.6%)
9-11th grade (no diploma)	645 (15.4%)	664 (16.1%)
High school graduate/GED	1202 (28.8%)	1063 (25.7%)
Some college/AA degree	1009 (24.2%)	1168 (28.3%)
College graduate or above	839 (20.1%)	800 (19.4%)
<i>Family Poverty-Income Ratio (PIR)</i>		
Mean ± SD	2.54 ± 1.57	2.40 ± 1.56
Median [IQR]	2.07 [1.21-3.98]	2.07 [1.13-3.67]
Below poverty line (PIR < 1.0)	771 (18.5%)	879 (21.3%)
<i>Pesticide Use, n (%)</i>		
Yes	726 (17.4%)	643 (15.6%)
No	3451 (82.6%)	3490 (84.4%)
<i>Smoking (ever ≥ 100 cigarettes), n (%)</i>		
Yes	2217 (53.1%)	1500 (36.3%)
No	1960 (46.9%)	2633 (63.7%)
<i>Depression (PHQ-9)</i>		
PHQ-9 score	2.88 ± 4.15	4.15 ± 5.02
<i>Thyroid Parameters</i>		
TSH (mIU/L)	1.93 ± 2.22	2.19 ± 5.69
Free T3 (pg/mL)	3.26 ± 0.39	3.10 ± 0.67
Free T4 (ng/dL)	0.80 ± 0.15	0.81 ± 0.20
Total T3 (ng/dL)	114.53 ± 22.01	113.13 ± 29.04
Total T4 (µg/dL)	7.71 ± 1.54	8.21 ± 1.76
Thyroglobulin (ng/mL)	13.92 ± 41.35	20.41 ± 81.39
<i>BP (mmHg)</i>		
Systolic BP 1	126.06 ± 17.20	122.39 ± 20.24
Diastolic BP 1	71.55 ± 13.17	68.12 ± 12.98
Systolic BP 2	124.81 ± 16.87	121.10 ± 19.81
Diastolic BP 2	71.12 ± 13.12	67.72 ± 13.20
Systolic BP 3	123.70 ± 16.62	120.06 ± 19.43
Diastolic BP 3	70.89 ± 13.40	67.36 ± 13.39
<i>Survey Cycle, n (%)</i>		
2007-2008	2,511 (60.1)	2,521 (61.0)
2009-2010	892 (21.4)	891 (21.6)
2011-2012	774 (18.5)	721 (17.4)

404 **B: LEMON Cohort (Leipzig, Germany; N = 227)**

	Men (n = 145)	Women (n = 82)
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Demographics		
Age: Young/Old, n (%)	108 (74.5) / 37 (25.5)	45 (54.9) / 37 (45.1)
BMI (kg/m ²)	24.43 ± 3.47	23.90 ± 3.93
Waist circumference (cm)	86.74 ± 11.69	80.25 ± 11.63
Smoking Status, n (%)		
Non-smoker	125 (86.2)	65 (79.3)
Occasional smoker	12 (8.3)	9 (11.0)
Smoker	8 (5.5)	8 (9.8)
Drug Test Result, n (%)		
Negative	135 (96.4)	73 (91.2)
Positive	5 (3.6)	7 (8.8)
Education Level, n (%)		
Gymnasium	119 (83.2)	57 (69.5)
Realschule	21 (14.7)	21 (25.6)
Hauptschule	3 (2.1)	4 (4.9)
Relationship Status, n (%)		
In relationship	100 (71.4)	49 (62.8)
Single	40 (28.6)	29 (37.2)
Psychological Measures		
Depression (Hamilton Scale)	2.11 ± 2.34	2.88 ± 2.88
Trait Anxiety (STAI)	36.48 ± 8.60	35.89 ± 8.60
Perceived Stress (PSQ Overall)	29.73 ± 15.28	30.75 ± 15.89
Social Stress Score (TICS Social scales)	5.43 ± 2.78	6.04 ± 3.73
Work Stress Score (TICS Work scales)	9.77 ± 4.53	9.49 ± 5.30
Chronic Stress (TICS Overall)	77.57 ± 37.38	82.28 ± 46.51
Thyroid		
TSH (mU/L)	1.70 ± 0.85	1.76 ± 2.55
BP (mmHg)		
BP1 Left Systole	135.19 ± 17.16	132.28 ± 23.69
BP1 Left Diastole	78.36 ± 11.40	79.94 ± 12.55
BP1 Right Systole	135.99 ± 17.10	130.72 ± 23.72
BP1 Right Diastole	78.01 ± 11.82	78.32 ± 13.17
BP2 Left Systole	132.95 ± 18.15	134.62 ± 26.79
BP2 Left Diastole	79.41 ± 10.88	81.34 ± 13.09
Lipid Profile		
Total Cholesterol (mmol/L)	4.75 ± 1.10	5.53 ± 1.24
LDL-C (mmol/L)	2.92 ± 0.96	3.30 ± 1.23
HDL-C (mmol/L)	1.47 ± 0.33	1.95 ± 0.49
LDL/HDL Ratio	2.10 ± 0.87	1.85 ± 1.01
Triglycerides (mmol/L)	1.47 ± 0.86	1.22 ± 0.62
Haematological		
RDW (%)	12.62 ± 2.12	12.66 ± 0.85

Data are mean ± SD for continuous variables and n (%) for categorical variables. NHANES depression used PHQ-9 = Patient Health Questionnaire-9 (range 0-27); PIR = Poverty-Income Ratio; LEMON age: Young (20-40 years) and Old (55-80 years); participants aged 40-55 were excluded by study design. Categorical percentages are based on available data; STAI = State-Trait Anxiety Inventory; PSQ = Perceived Stress Questionnaire; TICS = Trier Inventory for Chronic Stress.

411 **Table 2. Sex-Stratified Depression, Thyroid Hormone, and BP Associations in the NHANES Cohort**

Sex	Outcome / Path	Predictor / Mediator	β / ACME	SE	p	R ²
A. Significant depression and thyroid-to-blood-pressure regressions (adjusted for age, BMI, and survey year; men $n = 4,177$, women $n = 4,133$)						
Female	Free T4	Depression	-0.027	0.011	0.017	0.05
Female	Total T4	Depression	-0.028	0.013	0.029	0.03
Female	Mean DBP	Free T4	-0.081	0.017	<0.001	0.02
Female	Mean DBP	Total T4	-0.062	0.015	<0.001	0.02
Female	Mean SBP	Free T3	0.067	0.018	<0.001	0.30
Female	Mean DBP	Free T3	0.095	0.018	<0.001	0.02
Male	Mean DBP	Free T4	-0.107	0.019	<0.001	0.03
Male	Mean DBP	TSH	0.032	0.016	0.048	0.02
Male	Mean SBP	Free T3	0.073	0.017	<0.001	0.14
Male	Mean DBP	Free T3	0.101	0.019	<0.001	0.03
Male	Mean SBP	Total T3	0.041	0.015	0.005	0.14
Male	Mean DBP	Total T3	0.084	0.017	<0.001	0.03
B. Causal mediation of the depression effect on mean diastolic BP in women (no significant mediation in men)						
Female	Depression $\rightarrow$ Free T4 $\rightarrow$ DBP	Free T4 (12%)	0.00215	—	0.026	—
Female	Depression $\rightarrow$ Total T4 $\rightarrow$ DBP	Total T4 (10%)	0.00174	—	0.042	—
ACME, average causal mediation effect; values in parentheses are the proportion of the depression effect on diastolic BP mediated by each hormone. Mediation was estimated with 1,000 quasi-Bayesian simulations; both mediation effects were nullified at a sensitivity error correlation = 0.1. β , regression coefficient (Estimate); SE, standard error; SBP, systolic BP; DBP, diastolic BP.						

413 **Table 3. Sex-Stratified Stress, TSH, and BP Associations in the LEMON Cohort**

Sex / Group	Predictor	β	SE	p	R ²
A. Regressions of BP on psychological stress (significant and trend-level, $p < 0.10$; adjusted for age and BMI; males $n = 145$, females $n = 82$)					
Male	Trait anxiety (BP2 left diastole)	0.148	0.069	0.035	0.42
Male	TICS Chronic Worrying (BP2 left diastole)	0.129	0.061	0.038	0.42
Male	TICS Overall (BP1 left systole)	-0.107	0.058	0.066 (t)	0.33
Male	TICS Screening Scale (BP1 right diastole)	0.143	0.079	0.072 (t)	0.33
Male	Trait anxiety (BP1 right diastole)	0.141	0.0078	0.0073 (t)	0.33
Male	TICS Work Demands (BP1 right diastole)	0.117	0.068	0.086 (t)	0.33
Male	TICS Chronic Worrying (BP1 right diastole)	0.119	0.069	0.088 (t)	0.33
Female	Lack of Social Recognition (BP2 left diastole)	0.119	0.058	0.043	0.49
Female	Social Isolation (BP2 left diastole)	0.154	0.078	0.050 (t)	0.49
Female	PSQ Overall (BP1 right diastole)	0.189	0.098	0.056 (t)	0.30
Female	Work Overload (BP2 left diastole)	0.159	0.086	0.067 (t)	0.48
Female	Social Tension (BP2 left diastole)	0.116	0.064	0.073 (t)	0.48
Female	Pressure to Perform (BP2 left diastole)	0.131	0.077	0.094 (t)	0.48
Female	Work Discontent (BP1 right diastole)	0.161	0.095	0.095 (t)	0.29
B. Moderation of diastolic BP by TSH in women ($n = 82$); no significant moderation in men					
Female	Hamilton depression $\times$ TSH	0.213	0.100	0.037	0.49
Female	Chronic Worrying $\times$ TSH	0.207	0.101	0.043	0.50
C. TSH-stratified regression of right diastolic BP on psychological stress in women (adjusted for age and BMI)					
High TSH ($n = 13$)	TICS Chronic Worrying	0.307	0.095	0.010	0.73
High TSH ($n = 13$)	Hamilton depression	0.248	0.086	0.018	0.69
Normal TSH ($n = 52$)	TICS Chronic Worrying	-0.027	0.111	0.811 (ns)	0.20
Normal TSH ($n = 52$)	Hamilton depression	0.024	0.115	0.837 (ns)	0.20
Low TSH ($n = 15$)	TICS Chronic Worrying	0.203	0.118	0.113 (ns)	0.77
Low TSH ($n = 15$)	Hamilton depression	-0.181	0.180	0.337 (ns)	0.73
<i>All coefficients are from robust-Z scaled variables. A positive interaction coefficient indicates that the slope of stress on diastolic BP increases as TSH rises. BP2 left diastole denotes the second left-arm diastolic reading. β, regression coefficient (Estimate); SE, standard error; ns, non-significant p-value; t, trend-level, $p < 0.10$.</i>					

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